Sirolimus Treatment of an Infant With Intrathoracic Kaposiform Hemangioendothelioma Complicated by Life-threatening Pleural and Pericardial Effusions

Lucy Duan, MD, Samuele Renzi, MD,† Danielle Weidman, MD,† Nicolas Waespe, MD,†‡ Rose Chami, MD,§ David Manson, MD,‖ Michaela Cada, MD, MPH,† and Manuel Carcao, MD, MSc†*

Summary: Kaposiform hemangioendothelioma (KHE) is a rare infiltrative vascular tumor that may be associated with Kasabach-Merritt Phenomenon (KMP), which is a consumptive coagulopathy with potentially life-threatening thrombocytopenia. Management of KHE and KMP is challenging, and currently, there are no standardized validated treatment protocols. Mammalian target of rapamycin inhibitors have been shown to be effective in the treatment of KHE. We describe a term male who presented as a diagnostic dilemma with life-threatening pleural and pericardial effusions and severe thrombocytopenia. After extensive work-up the etiology for his condition was determined to be KHE with KMP. The patient was commenced on sirolimus and responded well to therapy with resolution of KMP.

Key Words: Kaposiform hemangioendothelioma, Kasabach-Merritt Phenomenon, sirolimus, rapamycin

(*J Pediatr Hematol Oncol* 2018;00:000–000)

Kaposiform hemangioendothelioma (KHE) is a rare vascular, infiltrative tumor typically encountered in infancy as a large (> 5 cm) cutaneous lesion with ill-defined borders located in the skin or soft tissue.[1] KHE may spontaneously decrease in size with time, but complete regression is uncommon.[2] KHE are typically located in the neck, axilla, groin, extremities, and trunk but can occur in non-cutaneous locations including the bone, mediastinum, and retroperitoneum. Lesions are usually solitary; however, multifocal lesions have been reported.[3,4] There are no reports implicating underlying genetic mutations, sex, or ethnicity bias in the etiology of KHE. Most cases present within the first 3 months of life with some cases diagnosed in utero and others after several years of life.[2,3]

KHE may be associated with Kasabach-Merritt Phenomenon (KMP), a potentially life-threatening consumptive coagulopathy.[5] Laboratory disturbances include profound thrombocytopenia (< 50,000/μL) and hypofibrinogenemia with elevated markers of coagulation activation including d-dimer and fibrin degradation products.

Received for publication April 29, 2018; accepted June 22, 2018.
From the Departments of *Paediatrics; †Paediatrics, Division of Haematology/Oncology; §Paediatric Laboratory Medicine; ‖Diagnostic Imaging, The Hospital for Sick Children, Toronto, ON, Canada; and ‡Swiss Childhood Cancer Registry, Institute of Social and Preventive Medicine, University of Bern, Switzerland.
The authors declare no conflict of interest.
Reprints: Lucy Duan, MD, Department of Pediatrics, The Hospital for Sick Children, 555 University Avenue, Toronto, ON, Canada M5G 1X8 (e-mail: lucy.duan@sickkids.ca).

Management of KHE associated with KMP can be challenging and currently there are no standardized validated treatment protocols.[6] Consensus derived first-line therapy for complicated KHE (eg, with pain, cellulitis, ulcerations, visceral/bone involvement, or cardiac dysfunction) and KHE associated with KMP was developed in 2013 through a survey of 24 vascular anomaly centers and a review of existing literature.[6] First-line therapy included vincristine with or without oral or intravenous corticosteroids.[6] Since 2013, mammalian target of rapamycin (mTOR) inhibitors have been shown to be safe and effective in the treatment of vascular tumors such as KHE and even more recently in the treatment of vascular malformations.[7,8]

We describe a newborn term male who presented as a diagnostic dilemma with life-threatening pleural and pericardial effusions and severe thrombocytopenia. A diagnosis of KHE complicated by KMP was made and the patient demonstrated partial response to oral sirolimus after several weeks of treatment.

CASE REPORT

A full-term male neonate was born at 39 weeks gestation to a 26-year-old G_2P_0 mother. She was blood group B positive and had a normal prenatal ultrasound at 20 weeks gestation. At 36 weeks gestation, prenatal ultrasound showed polyhydramnios and the fetus was found to have severe bilateral pleural effusions, left greater than right, with mediastinal deviation. As a result, the fetus underwent insertion of bilateral pleuroamniotic shunts in utero. The baby was delivered with vacuum assistance after spontaneous rupture of membranes; birth weight was 3.18 kg. There was meconium present at delivery and APGAR scores were 7, 8, and 9 at 1, 5, and 10 minutes, respectively. Both pleuroamniotic shunts were clamped at birth and removed at 3 minutes of life. The baby was admitted to the neonatal intensive care unit. Initial examination demonstrated a well-grown male infant with no dysmorphisms or cutaneous anomalies.

On day 8 of life, a right-sided chest tube was inserted due to reaccumulation of pleural effusion. Pleural fluid analysis showed chylous content. On day 16 of life, the chest tube drainage subsided, and the chest tube was removed. On day 30 of life, the infant developed increased work of breathing requiring transient continuous positive airway pressure. Once weaned back to room air, the infant was transferred to a pediatric inpatient unit for further investigation.

Complete blood count on day 1 of life showed a platelet count of 157,000/μL, which dropped to 46,000/μL by day 15 of life and to 23,000/μL on day 23 of life. In addition to this gradually worsening thrombocytopenia, there were increased reticulocytes, markedly elevated lactate dehydrogenase of 2176 U/L, and presence of schistocytes (fragments) on the blood smear. There were signs of a consumptive coagulopathic process including low fibrinogen

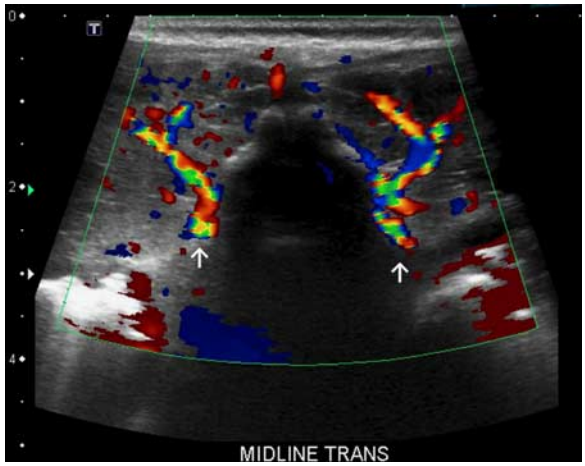

FIGURE 1. Curvilinear transducer with color Doppler image from a posterior approach shows increased vascularity (arrows) to the paraspinal dorsal muscle groups. full color online

(0.8 g/L) and elevated d-dimer (>4 μg/mL fibrinogen equivalent units). The patient required transfusions of multiple blood products including platelets, fresh frozen plasma, and cryoprecipitate with minimal improvement in the platelet count and coagulopathy.

The following investigations were normal: ADAMTS13 activity, neonatal alloimmune thrombocytopenia testing, HLA antibody testing, and Noonan syndrome genetic testing. Echocardiogram showed patent foramen ovale and closed ductus arteriosus. Ultrasounds of thyroid and abdomen did not show any anomaly. Total-body magnetic resonance imaging (MRI) without contrast was performed at 1 month of life to search for a vascular malformation/tumor as a source of the consumptive coagulopathy, and demonstrated pleural effusions and a small amount of ascites with no vascular anomalies.

On the basis of the results of laboratory investigations including thrombocytopenia, low fibrinogen, elevated d-dimer, and minimal response to platelet transfusions, there continued to be a high clinical suspicion of KMP. As such, previous imaging was repeated. This included an abdominal ultrasound in conjunction with a spinal ultrasound to screen for intraspinal contents. This revealed increased vascularity and hyperemia within the dorsal chest wall musculature. A dedicated MRI (with contrast) of this area was then performed, which revealed an extensive infiltrative vascular lesion involving the bilateral paraspinal musculature, prevertebral spaces, posterior extrapleural space, mediastinum, thymus, and neck with intense arterial enhancement. The lesion encased the thoracic aorta, great vessels, esophagus, thoracic trachea, and mainstem bronchi. The precise size of the lesion was not reported due to its extent and infiltrative nature (Figs. 1, 2A, B).

On the basis of the clinical and radiologic presentation, KHE was presumed to be the most likely diagnosis. Biopsy was not initially performed due to bleeding risk. The patient was started on prednisone (2 mg/kg/d) and oral sirolimus (0.8 mg/m^2/dose twice daily) on day 45 of life. There was no clinical or laboratory improvement after the first month of treatment, and the patient continued to require weekly red blood cell transfusions and frequent platelet transfusions. He developed recurrent bilateral pleural effusions that required multiple admissions to the pediatric intensive care unit for continuous positive airway pressure, and 6 chest tube insertions with serosanguineous drainage. In addition, on day 79 of life, he had pericardiocentesis with placement of a pericardial drain for a large circumferential pericardial effusion with signs of early tamponade. As his condition remained life-threatening and as he did not initially appear to respond to therapy, a surgical biopsy of the lesion was performed to rule out other potential entities. Biopsy findings confirmed the diagnosis of KHE (Figs. 3A–C). Histopathologic features included infiltrating nodules, sheets of variably spindled endothelial cells, focal immunopositivity for lymphatic endothelial markers, nuclear atypia, microthrombi, hemosiderin deposition, fibrosis, and abnormal lymphatic channels. With continued treatment, the patient slowly began to improve and was well enough for discharge from hospital at 3.5 months of life, was transfusion independent, had no evidence of further effusions.

The infant continued on sirolimus at the same dose as an outpatient, targeting blood levels of 5 to 15 μg/L. Prednisone was weaned off at 4.5 months of life. A repeat MRI with contrast performed after 7 months of sirolimus therapy showed significant reduction in the size of the original KHE (Fig. 4). The patient continues on the same nominal dose of sirolimus, without adjustments for weight gain. He is doing well clinically and will have a repeat MRI after 2 years of sirolimus therapy. If the lesion continues to regress sirolimus will be slowly discontinued at that time.

DISCUSSION

We present a case of a newborn male with KMP secondary to intrathoracic KHE without cutaneous involvement, complicated by prolonged pericardial and pleural effusions leading to life-threatening respiratory complications. He had a good response to sirolimus therapy. Intrathoracic KHE is rare. In a large retrospective review of 107 patients with KHE at Boston Children's Hospital only 9 of the 107 patients had intrathoracic KHE.[3] Compared with superficial lesions, intrathoracic KHE lesions are 18-fold

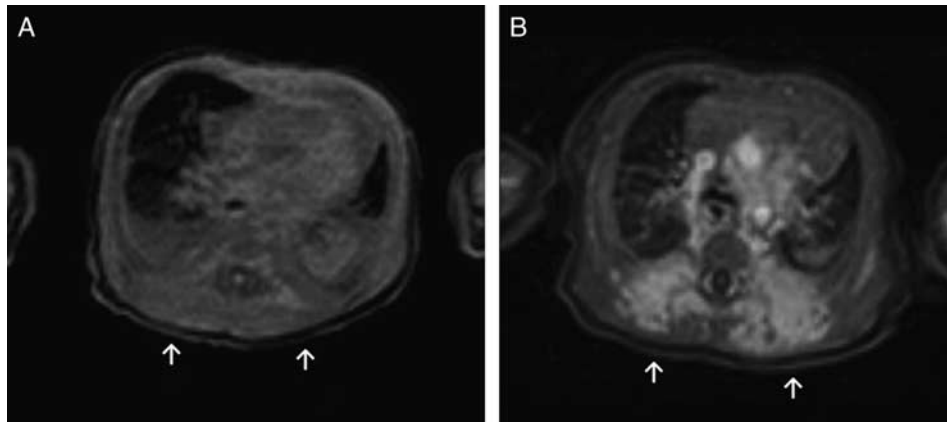

FIGURE 2. Pregadolinium-enhanced (A) and postgadolinium-enhanced (B) T1 fat-suppressed images show extensive enhancement (arrows) throughout the posterior thoracic musculature. The enhancement pattern is lobulated, consistent with an infantile kaposiform hemangioendothelioma.

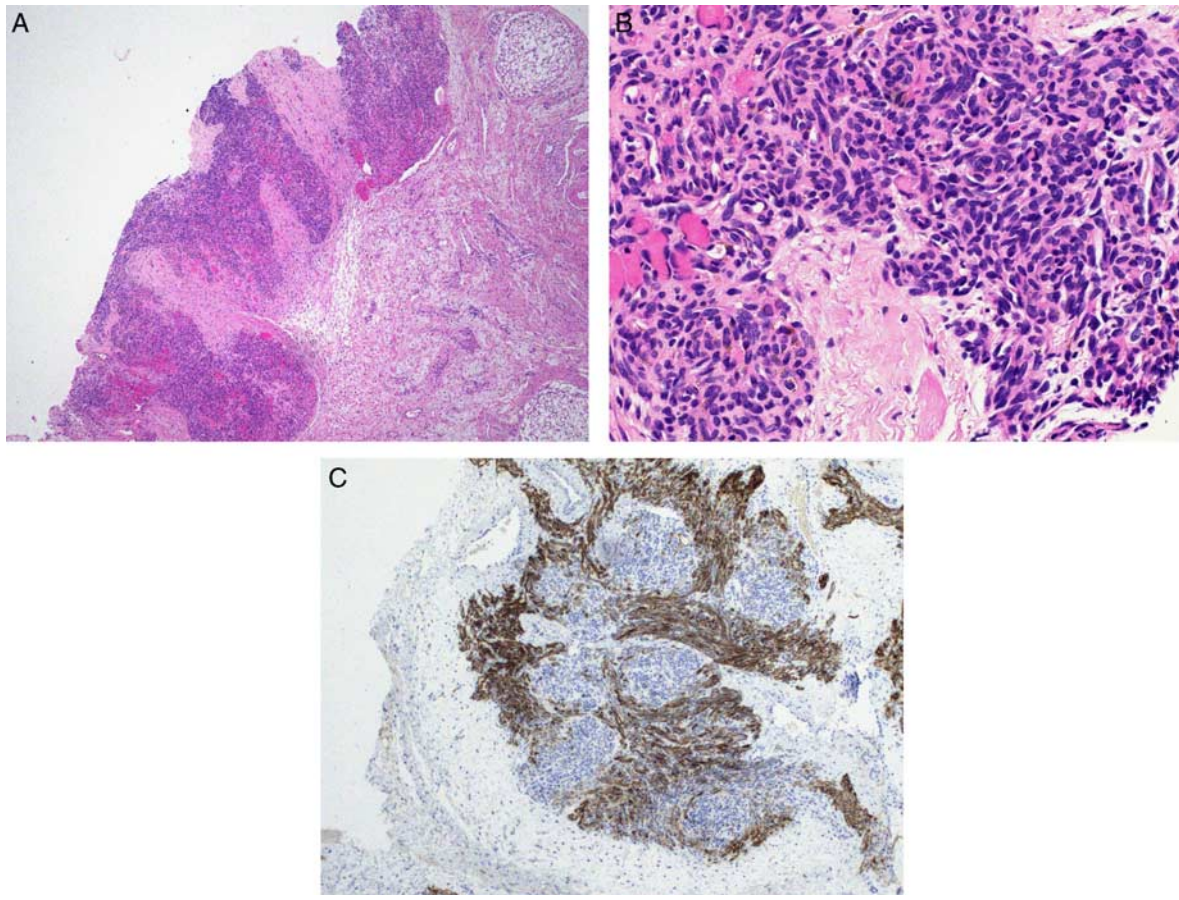

FIGURE 3. A, Multinodular tumor composed of sheets of spindled cells, well-formed capillary-like vessels and occasional crescent-shaped vascular spaces. Hematoxylin and eosin stain, ×2 magnification. B, "Glomeruloid" clusters of rounded to epithelioid endothelial cells. Hematoxylin and eosin stain, ×20 magnification. C, D2-40 (lymphatic marker) mainly stained the neoplastic spindled cells, ×4 magnification. full color online

more likely to manifest KMP, and these patients usually present with clinical respiratory distress.[3] In addition, only 11% of all KHE have been reported to have no overlying skin changes.[3] Our patient's clinical presentation was unique in that the infant developed life-threatening pleural and pericardial effusions, which are rare complications of KMP.[3,9] The mechanism of the development of pleural and pericardial effusions is not completely understood, but given the chylous content of the pleural fluid, it was thought to be secondary to blockage of lymphatic drainage by the mass.[10]

Platelet transfusions have been shown to be of minimal benefit in patients with KMP.[6] In addition, platelets can be retained within the KHE and result in enlargement of the mass.[11] This may have occurred in our patient before the diagnosis of KHE being made. Our patient's transfusion-refractory thrombocytopenia and coagulopathy prompted repeat MRI imaging—this time with contrast. This then confirmed the diagnosis. Once a diagnosis of KHE was made, platelet transfusions were restricted to only surgical procedures or in the case of bleeding.

MRI is the imaging modality of choice to demonstrate and evaluate the extent of such masses.[3] T2 weighted MRI typically demonstrates a poorly marginated area of abnormal increased T2 weighted signal, and tubular flow voids of the increased vascularity may be seen.[3] Flow sensitive and gadolinium-enhanced sequences can help to show the increased vascularity. Whole body MRI without contrast can miss even large lesions. This occurred in our case. Once the diagnosis of KHE was made, the first MRI (without contrast) that failed to show the lesion was rereviewed. Indeed, hyperintensity in the spinal musculature was seen but this had initially been interpreted as compression artefacts due to the supine positioning of the child. Diagnosis of KHE was finally suspected based on the characteristic imaging findings by dedicated gadolinium-enhanced MRI of the region of interest (Figs. 1/, 2A, B, 4) and a diagnosis was confirmed with histopathology (Figs. 3A–C).

Recently, a clinicopathologically distinct anomaly kaposiform lymphangiomatosis (KLA) was described and is characterized by clinical intrathoracic disease with effusions and respiratory symptoms, as well as histologic findings of spindled lymphatic endothelial cells.[12] Our patient's unique presentation with pericardial and pleural effusions leading to multiple episodes of respiratory decompensation requiring noninvasive ventilation was atypical of KHE and raises the possibility of KLA. However, a review of histologic features on the biopsy showed features characteristic of classic KHE (Figs. 3A–C) and not KLA.

The recent addition of mTOR inhibitors to the management of vascular tumors and malformations has significantly improved the therapeutic options for patients, particularly when a lymphatic component is present.[7] The

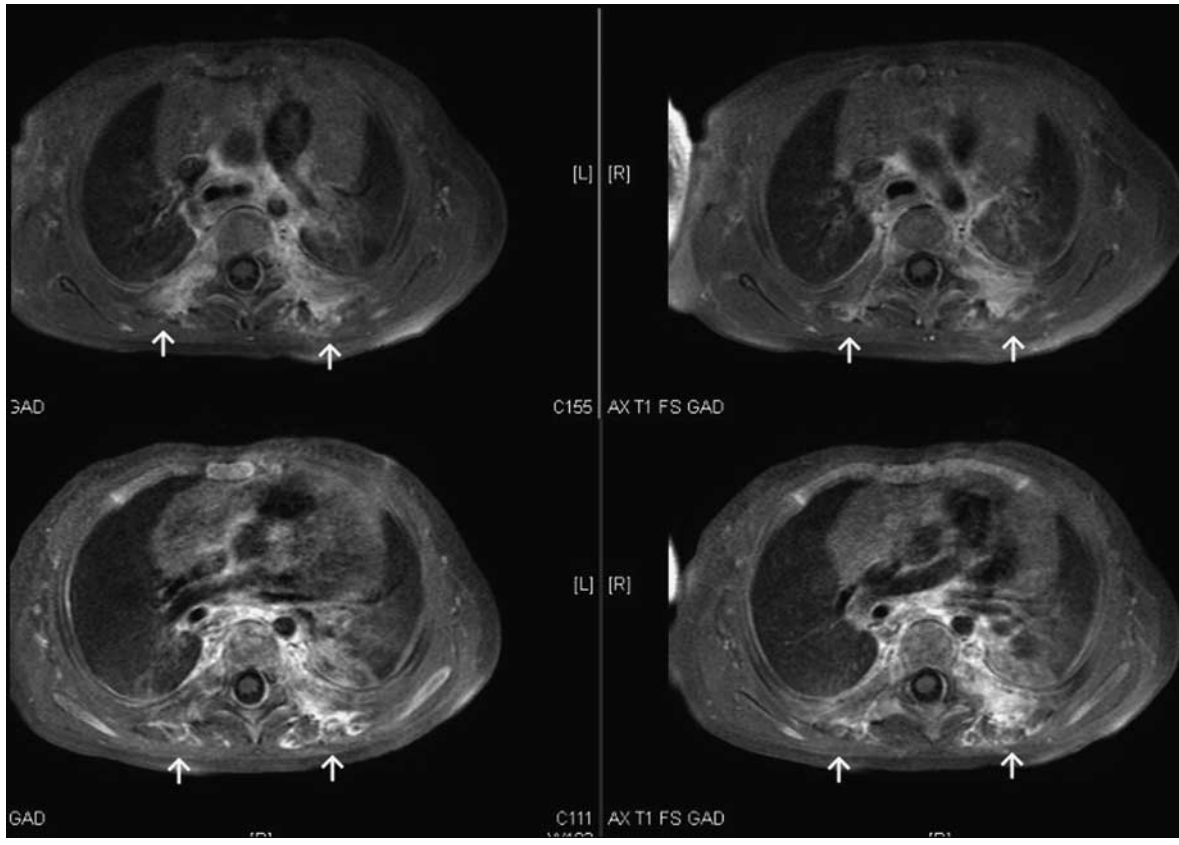

FIGURE 4. Follow-up gadolinium T1 fat-suppressed magnetic resonance imaging images show a persistent lesion (arrows) that is less extensive and less infiltrative.

mTOR inhibitor sirolimus is an oral medication that can be taken in the outpatient setting, with significantly less side effects than the previous first-line therapies of vincristine and/or steroids. Sirolimus has been used in the treatment of KHE associated with KMP, leading to reduction in tumor size and an increase in platelet counts; however, doses, duration of therapy, and utility of targeting sirolimus levels have not been standardized.[13,14] Sirolimus has been shown to inhibit lymphangiogenesis, which in turn decreases platelet trapping.[15] Our patient was started on sirolimus at a dose of 0.8 mg/m^2/dose twice daily, targeting serum levels of 5 to 15 μg/L. This dose was based on the publication of the phase II trial conducted by Adams et al[7] which included 57 patients treated with sirolimus for either vascular tumors (13 of which had KHE) or malformations. Adams et al[7] reported that all patients with KHE with KMP demonstrated partial response to sirolimus.

A systematic review of the efficacy and safety of mTOR inhibitors in the treatment of vascular anomalies revealed that sirolimus was the most common agent used and was effective and well tolerated, although dosage was heterogenous.[16] A retrospective review evaluated the response to sirolimus in patients with vascular tumors and malformations and found a response rate of 80.4% with improvement in radiologic imaging and symptom reduction after a median of 10 weeks.[17] A recent multicenter retrospective cohort study was conducted in patients with progressive KHE treated with sirolimus.[18] Patients without KMP were treated with sirolimus alone and patients with KMP received sirolimus (0.8 mg/m^2 twice daily, adjusted to attain trough levels of 10 to 15 ng/mL) and prednisolone.[18] In all patients on dual therapy, prednisolone was tapered and patients continued on sirolimus treatment alone.[18] Overall, the above studies have shown that the response to sirolimus is not immediate, and that the duration of therapy is not known. Furthermore, it is not known what doses are required or what is the appropriate sirolimus target range. These questions regarding sirolimus use in KHE remain to be explored.

Our patient was started on sirolimus following MRI imaging consistent with KHE. After 2 months of being on sirolimus therapy he was no longer severely thrombocytopenic, and a 6-month repeat MRI showed significant reduction in the size of the mass (Fig. 4). This case outlines the importance of aggressively searching for an underlying vascular tumor even without skin findings in the presence of suspected KMP, and utilizing specific imaging modalities in diagnosing a vascular tumor. Our patient had an overall good, but not immediate, response to sirolimus, though there is no consensus in the literature for the optimal duration of treatment, or the long-term prognosis of KHE once treatment is discontinued. Further studies investigating these aspects are key for optimal management of these patients.

REFERENCES

1. Zukerberg LR, Nickoloff BJ, Weiss SW. Kaposiform hemangioendothelioma of infancy and childhood. An aggressive

neoplasm associated with Kasabach-Merritt syndrome and lymphangiomatosis. *Am J Surg Pathol*. 1993;17:321–328.
2. Enjolras O, Mulliken JB, Wassef M, et al. Residual lesions after Kasabach-Merritt phenomenon in 41 patients. *J Am Acad Dermatol*. 2000;42:225–235.
3. Croteau SE, Liang MG, Kozakewich HP, et al. Kaposiform hemangioendothelioma: atypical features and risks of Kasabach-Merritt phenomenon in 107 referrals. *J Pediatr*. 2013;162:142–147.
4. Deraedt K, Vander Pooten V, Van Geet C, et al. Multifocal kaposiform hemangioendothelioma. *Virchows Arch*. 2006;448:843–846.
5. Kasabach H, Merritt K. Capillary hemangioma with extensive purpura: report of a case. *Am J Dis Child*. 1940;59:1063–1070.
6. Drolet BA, Trenor CC III, Brandao LR, et al. Consensus-derived practice standards plan for complicated kaposiform hemangioendothelioma. *J Pediatr*. 2013;163:285–291.
7. Adams DM, Trenor CC III, Hammill AM, et al. Efficacy and safety of sirolimus in the treatment of complicated vascular anomalies. *J Pediatr*. 2016;137:e20153257.
8. Hammill AM, Wentzel M, Gupta A, et al. Sirolimus for the treatment of complicated vascular anomalies in children. *Pediatr Blood Cancer*. 2011;57:1018–1024.
9. Wallenstein MB, Hole MK, McCarthy C, et al. Mediastinal kaposiform hemangioendothelioma and Kasabach-Merritt phenomenon in a patient with no skin changes and a normal chest CT. *J Pediatr Hematol Oncol*. 2014;31:563–567.
10. Jiang J, Li Y, Hu C, et al. Primary pleural intermediate hemangioendothelioma with pleural effusion as the only manifestation. *J Thorac Dis*. 2016;8:E369–E373.
11. Phillips WG, Marsden JR. Kasabach-Merritt syndrome exacerbated by platelet transfusion. *J R Soc Med*. 1993;86:231–232.
12. Croteau SE, Kozakewich HPW, Perez-Atayde AR, et al. Kaposiform lymphangiomatosis: a distinct aggressive lymphatic anomaly. *J Pediatr*. 2014;164:383–388.
13. Boccara O, Puzenat E, Proust S, et al. Sirolimus effects on Kasabach-Merritt phenomenon coagulopathy. *Br J Dermatol*. 2018;178:e114–e116.
14. Tasani M, Ancliff P, Glover M. Sirolimus therapy for children with problematic Kaposiform hemangioendothelioma and tufted angioma. *Br J Dermatol*. 2017;177:e344–e346.
15. Huber S, Bruns CJ, Schmid G, et al. Inhibition of the mammalian target of rapamycin impedes lymphangiogenesis. *Kidney Int*. 2007;71:771–777.
16. Nadal M, Giraudeau B, Tavernier E, et al. Efficacy and safety of mammalian target of rapamycin inhibitors in vascular anomalies: a systematic review. *Acta Derm Venereol*. 2016;96:448–452.
17. Triana P, Dore M, Cerezo VN, et al. Sirolimus in the treatment of vascular anomalies. *Eur J Pediatr Surg*. 2017;27:86–90.
18. Ji Y, Chen S, Xiang B, et al. Sirolimus for the treatment of progressive kaposiform hemangioendothelioma: a multicenter retrospective study. *Int J Cancer*. 2017;141:848–855.